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Role of the venous system in hemodynamics during ultrafiltration and bicarbonate dialysis

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Role of the venous system in hemodynamics during ultrafiltration and bicarbonate dialysis. A reduced venous compliance (VC) and inadequate venoconstriction may impair hemodynamics during hemodialysis, the first by impairing plasma volume preservation and by inducing a steep fall in central venous pressure (CVP) during minor plasma volume loss, the second by inadequate mobilization of hemodynamically inactive blood volume. For the protocol A, the relation between VC, the fall in plasma volume and the decline in central venous pressure (CVP) was assessed in 12 hemodialysis (HD) patients, aged 40 to 74 years, during isolated ultrafiltration (UF). The patients were ultrafiltrated for one hour at an UF rate of 1 to 1.5 liter/hr. VC was measured by strain gauge plethysmography with direct i.v. pressure measurements. CVP was assessed directly via a subclavian catheter. PVP was measured using the serial hematocrit method. VC correlated inversely with the fall in plasma volume ($r = -0.66$; $P < 0.025$) and with the fall in CVP (corrected for UF volume) ($r = -0.62$; $P < 0.025$). In the protocol B, the constriction of veins and resistance vessels was assessed sequentially during isolated UF and during UF combined with bicarbonate HD (UF + HD) by measuring the change in venous tone (VT) and vascular resistance (FVR) of the forearm. Twelve HD patients were studied (age 30 to 64 years). VT and FVR were measured using strain gauge plethysmography. The UF rate was equal during isolated UF and UF + HD (1 liter/hr). In six patients, the measurements were started with isolated UF and in six patients with UF + HD. After the investigation, the heart rate response towards a Valsalva maneuver was assessed. The fall in plasma volume was equal during isolated UF and UF + HD ($-5.7 \pm 4.9\%$ and $-7.2 \pm 2.7\%$, respectively). In all patients, VT and FVR increased during isolated UF ($P < 0.005$), but remained stable during UF + HD. No significant correlation was observed between the Valsalva ratio and the vascular reaction during isolated UF and UF + HD. We conclude that, in protocol A, a reduction in VC impairs plasma volume preservation during UF and leads to a steeper decline in CVP with a similar UF volume. In the protocol B, during UF combined with HD, the constriction of veins and resistance vessels is significantly reduced compared to the vascular reaction during isolated UF, which may play an important role in the occurrence of hypotension during HD. Tests studying the heart rate response in hemodialysis patients do not have a predictive value for the vascular response during hemodialysis.

Hypotensive periods occur frequently during hemodialysis, and are a major cause of morbidity in patients treated with chronic intermittent hemodialysis [1]. Both an impaired preservation of plasma volume and inadequate cardiovascular regulation mechanisms are important factors in the loss of blood pressure control during hemodialysis [1, 2].

The venous system plays an important role in the hemodynamic regulation of the human body. It serves both as a conductance system for the backflow of hemodynamically active ('stressed') blood from the peripheral vessels to the heart and as a blood reservoir for hemodynamically inactive ('unstressed') blood volume [3].

During plasma volume depletion, a reduction in the volume/pressure relationship of the stressed compartment (venous compliance) can have a negative impact on hemodynamic stability during dialysis both by inducing a steep fall in central venous pressure [4] and by impairing capillary refill during a decline in plasma volume [5]. In a previous study we showed that VC was reduced in hypertensive hemodialysis patients [6].

In addition to venous compliance (VC), the translocation of blood from the unstressed to the stressed compartment by active or passive venoconstriction is of the utmost importance in the regulation of venous return to the heart and therefore in blood pressure control [3]. We observed in a previous study that venoconstriction during an efferent sympathetic stimulus was normal in hemodialysis patients [6]. However, a dysfunction of the baroreceptor reflex arc, demonstrated by an impaired response to the Valsalva maneuver [7] or an acute disturbance of the vascular reaction during hemodialysis [8] might result in impaired active venoconstriction with an ensuing decrease in venous return. In addition, the hemodialysis treatment itself might induce an acute impairment of the vascular reaction, a view supported by the superior hemodynamic stability which is observed when fluid is removed by isolated ultrafiltration (UF).

In this study the relation between VC, the fall in central venous pressure (CVP) and the decline in plasma volume in patients treated with chronic intermittent hemodialysis was evaluated during isolated UF.

Furthermore, in a second protocol, the reaction of the veins and resistance vessels to a decline in plasma volume was assessed during isolated UF and during UF combined with bicarbonate dialysis. In addition, the vascular reaction was related towards the response to the Valsalva maneuver.

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Table 1. Individual values for age, existence of hypertension, venous compliance (VC), and for the ultrafiltration rate (UF rate), the decline in central venous pressure (−CVP) and plasma volume (−PV) during isolated UF (protocol A)

Patient	Age *years*	Hypertension	VC *ml/100 ml/mm Hg*	UF rate *ml/hr*	−CVP *mm Hg/liter*	−PV *%/liter*
1	67	+	0.012	1000	3.8	14.6
2	61	−	0.072	1000	2.6	7.6
3	59	−	0.075	1000	1.2	10.0
4	71	+	0.030	1500	3.3	11.8
5	44	−	0.051	1000	2.2	9.9
6	72	−	0.044	1300	1.5	8.3
7	61	−	0.042	1300	1.9	11.4
8	58	+	0.040	1300	2.8	8.0
9	74	+	0.034	1000	4.4	9.5
10	40	+	0.046	1000	2.6	9.5
11	61	−	0.062	1000	2.6	7.0
12	47	−	0.084	1000	2.2	8.8

Methods

General patient characteristics

Clinically stable patients treated by chronic intermittent hemodialysis were enrolled in the study. Exclusion criteria were acute infectious diseases, diabetes mellitus, severe coronary (NYHA II or more) or valvular heart disease and compromised left ventricular function (ejection fraction 30% or less).

Prior to studies, all subjects were asked to refrain from smoking or drinking caffeine containing beverages during an overnight period. Antihypertensive medication was stopped 48 hours before the study. Patients treated with angiotensin converting enzyme inhibitors were excluded. All subjects gave their informed consent and the study was approved by the Ethics Committee of the Maastricht University Hospital.

Protocol A. Influence of VC on the fall in plasma volume and CVP during isolated UF

Patients. Twelve hemodialysis patients were studied (5 males, 7 females). The mean age of the patients was 60 (range 40 to 74) years. The mean duration of hemodialysis treatment had been 1.8 (range 0.3 to 4.2) years. The mean body surface area of the patients was 1.77 (range 1.31 to 2.21) mm/m^2. The mean albumin level was 36 (range 23 to 45) g/liter, the mean hemoglobin level 5.7 (range 4.3 to 6.8) mmol/liter.

As shown in Table 1, seven patients were normotensive, defined as a post-dialytic blood pressure below 140/80 for at least six consecutive months without the use of antihypertensive medication [9], whereas five patients were hypertensive (post-dialytic blood pressure > 150/90 after dialysis). No patient used antihypertensive medication.

Study protocol. The patients were studied on the regular day of their dialysis scheme. The patients were 1 to 3 kg above their optimal dry weight, assessed by echography of the inferior caval vein [10]. Before the measurements were started, the patients had been supine and resting for 30 minutes. They were ultrafiltrated without dialysis for one hour at a rate of 1000 to 1500 ml/hr. No patient was ultrafiltrated below his/her optimal dry weight. A Gambro AK 100 dialysis apparatus and hemophane membranes (GFS 12; Gambro) were used. Blood pressure and heart rate were recorded continuously (Finapres; Ohmeda 2300; Lameris) [11].

CVP was monitored using a catheter (Permcath; Quinton; internal diameter 2 mm) which was inserted through the subclavian vein and positioned in the right atrium. The location of the catheter was checked by X-ray. The catheter was connected to a pressure dome (Hewlett-Packard) positioned at the height of the right atrium, which was considered 5 cm under the sternal angle. CVP was recorded continually (Hewlett-Packard 78205 C pressure monitor). The decline in plasma volume during UF was assessed by the serial hematocrit (Hct) method and calculated according to the following formula: Δplasma volume = $(100/100 - Hct_{before}) \times (100\,[Hct_{before} - Hct_{after}]/Hct_{after})$ [12].

Both the fall in CVP and the decline in plasma volume were corrected for the total ultrafiltrated volume (expressed as mm Hg/liter and %/liter, respectively).

Blood samples were taken in ice-chilled tubes before and after UF for determination of noradrenaline levels (HPLC method; inter-assay variance <8%). Furthermore, blood samples were taken for determination of plasma colloid osmotic pressure (Wescor 4400 Colloid Osmometer) and osmolality (Wescor 5500 Vapor Pressure Osmometer).

The morning after dialysis, VC was measured by strain gauge plethysmography [6, 13] (Periflow, Janssen Scientific Instruments) with direct intravenous pressure measurements (intraday variability 8.1%; inter-day variability 11.1%). The study was performed in a temperature controlled room (20 to 23°C) with the patient in supine position and the arm at heart level. A cuff was applied to the upper arm. The change in arm volume was measured using a mercury filled strain gauge, applied to the thickest part of the forearm. The peripheral venous pressure was measured through an intravenous cannula (internal diameter 1 mm; Venflon) inserted into an antecubital vein. Peripheral venous pressure was measured the same way as described above for CVP. After a 15 minute rest, the arm cuff was inflated at a pressure of 25 mm Hg and was kept inflated for three minutes. Hereafter, the arm cuff was deflated for two minutes. The same procedure was followed at cuff pressures of 30, 35, 40 and 45 mm Hg. The volume/pressure ratio at each cuff pressure was obtained after deflation of the arm cuff in order to exclude the effect of capillary filtration. VC was defined as the slope of the regression curve, constructed from the obtained volume/pressure ratios at the subsequent cuff pressures [14].

The fluid status of the patients was assessed by echographic estimation of the inferior caval vein diameter, corrected for body surface area [10] (vena cava diameter at normovolemia = 8 − 11.5 mm/m^2).

Protocol B. Reaction of the veins and resistance vessels during isolated UF and during UF combined with dialysis

Patients. Twelve hemodialysis patients were investigated (7 males, 5 females). The mean age of the patients in this group was 47 (range 30 to 64) years. The mean time on hemodialysis had been 3.7 (range 0.2 to 14.0) years. The mean hemoglobin level was 6.7 (range 4.0 to 8.7) mmol/liter, the mean albumin level 39 (range 27 to 47) g/liter. Three patients (no. 1, 6 and 8) were treated with calcium entry blockers (Table 3).

Study protocol. The patients were studied on the regular day of their dialysis scheme. Prior to the measurements being started, patients had been supine and resting for 30 minutes. For 45 minutes isolated UF was performed, whereas for 45 minutes UF was combined with hemodialysis. The UF rate was 1000 ml/hr during isolated UF as well as during UF combined with hemodialysis.

In six patients, the investigation was started with isolated UF, followed by UF combined with dialysis (sequential UF dialysis), while in the other six patients the investigation was started with UF combined with dialysis, followed by isolated UF (sequential dialysis-UF).

A Gambro AK-100 dialysis apparatus and hemophane membranes (GFS 12; Gambro) were used. The composition of the used dialysis fluid was: sodium 141 mmol/liter, potassium 2.0 mmol/liter, bicarbonate 34 mmol/liter, acetate 3 mmol/liter, calcium 1.75 mmol/liter, magnesium 0.5 mmol/liter, chloride 108 mmol/liter. The temperature of the dialysate was 37.5°C. Blood pressure and heart rate were recorded continuously during the study with the Finapres device.

Active venoconstriction was estimated in terms of changes in venous tone (pressure/volume ratio) of the forearm. Venous tone is expressed in reciprocal terms (mm Hg/ml/100 ml) compared with VC (ml/100 ml/mm Hg). Venous tone and forearm blood flow were assessed by strain gauge plethysmography with direct intravenous pressure measurements. The arm cuff, strain gauge and intravenous catheter were applied as previously described [6]. For the estimation of venous tone, the pressure/volume ratio was recorded at a cuff pressure of 40 mm Hg and after deflation of the arm cuff (intra-day reproducibility 11.9%).

To assess forearm blood flow, a cuff pressure of 50 mm Hg was used. The hand circulation was not occluded because of the presence of the Finapres device at the ipsilateral finger. The cuff was inflated 5 msec after the R-top of the electrocardiogram. An inflation/deflation ratio of 3:2 heart beats was used. Flow was estimated using a computerized integrator [13]. Venous tone and forearm blood flow were recorded every 15 minutes during the study. Forearm vascular resistance (FVR) was calculated by dividing the mean arterial pressure by the forearm blood flow.

Blood samples for noradrenaline, colloid osmotic pressure, osmolality and hematocrit were obtained before the study, after isolated UF and after UF combined with dialysis. The fall in plasma volume was recorded using the serial hematocrit method [12]. Furthermore, the potassium and sodium concentration was determined before the investigation and after UF combined with dialysis.

Table 2. Hemodynamic parameters before and after ultrafiltration (protocol A)

	Before	After	*P*
Central venous pressure *mm Hg*	8.0 (5.9)	4.7 (4.4)	<0.001
Decline in plasma volume *%*		−10.8 (4.4)	<0.001
Mean blood pressure *mm Hg*	95.9 (9.6)	93.7 (16.7)	
Heart rate *beats/min*	86.9 (12.1)	86.6 (17.5)	
Noradrenaline *nmol/liter*	4.5 (4.4)	6.3 (5.6)	<0.05
Osmolality *mOsm/kg*	291.7 (12.8)	293.1 (12.1)	
Colloid osmotic pressure *kPa*	2.6 (0.3)	2.9 (0.3)	<0.001

Values expressed as mean (SD).

After the investigation, a Valsalva maneuver was performed by expiration at a pressure of 40 mm Hg for 15 seconds with simultaneous ECG recording [15]. The Valsalva ratio was expressed as the ratio between the longest R-R interval during the release phase to the shortest R-R interval during the strain phase.

Statistical analysis

The values are expressed as mean (±SD). Correlations between variables were evaluated by linear regression analysis. Protocol A used a multivariate regression analysis with stepwise inclusion to assess the relative importance of factors influencing the fall in plasma volume and the decline in CVP. Protocol B used Friedman's analysis of variance to assess overall differences in the obtained parameters between the basal state and the subsequent treatment modes. When overall differences were significant, Wilcoxon's signed-rank test was used to analyze specific differences between the basal state and the different treatment modes.

Results

Protocol A. Influence of VC on the fall in plasma volume and CVP during isolated UF

Change in hemodynamic parameters. The individual data are presented in Table 1, and the summarized data before and after UF are presented in Table 2. Both plasma volume and CVP fell significantly during UF ($P < 0.001$). Noradrenaline levels rose significantly ($P < 0.05$), whereas blood pressure and heart rate remained stable. Osmolality remained stable, and the colloid osmotic pressure increased ($P < 0.01$). The rise in colloid osmotic pressure was significantly related to the decline in plasma volume ($r = 0.75$; $P < 0.01$).

Correlation between VC and the decline in CVP and plasma volume. Mean values for the vena cava diameter index and VC the day after dialysis were 8.4 (±3.4) mm/m^2 and 0.049 (±0.021) ml/100 ml/mm Hg, respectively. VC was inversely, though not significantly, related to the age of the patients ($r = -0.45$; $P = 0.07$). VC was significantly reduced in hypertensive patients compared to normotensive patients ($P < 0.025$). VC was inversely related to CVP before dialysis ($r = -0.55$; $P < 0.05$). Mean peripheral venous pressure the day after dialysis was 8.8 (±3.2) mm Hg.

VC correlated inversely with the fall in CVP during UF ($r = -0.62$; $P < 0.025$; Fig. 1), whereas the decline in plasma volume ($r = 0.39$) and UF rate ($r = 0.02$) were not. When multivariate regression analysis (Table 2) was used to assess the effect of

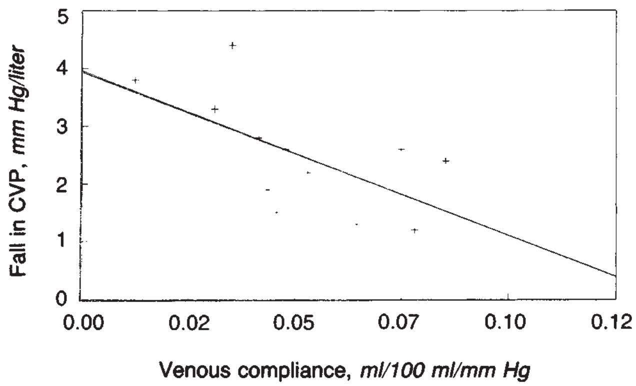

Fig. 1. *Relation between VC and the fall in CVP during isolated UF.* The fall in CVP was corrected for UF-volume. $r = -0.62$; $P < 0.025$.

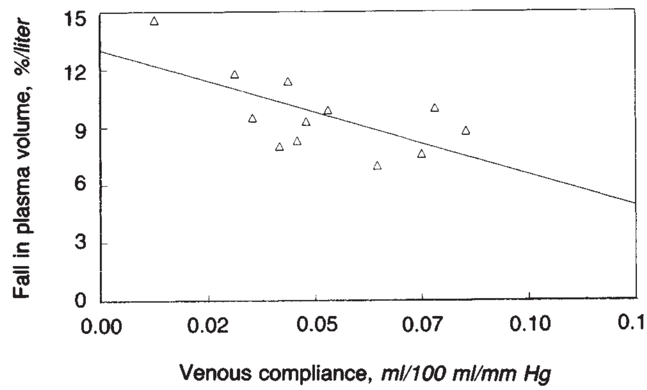

Fig. 2. *Relation between VC and the fall in plasma volume during isolated UF.* $r = -0.66$; $P < 0.025$. The fall in plasma volume was corrected for UF-volume.

Table 3. Individual values for age, Valsalva ratio and the change in venous tone (ΔVT) and forearm vascular resistance (ΔFVR) during the different treatment modes (protocol B)

Patient	Age *years*	VR	ΔVT (isolated UF) *mm Hg/ml/100 ml*	ΔVT (UF + dialysis) *mm Hg/ml/100 ml*	ΔFVR (isolated UF) *mm Hg/ml/100 ml/sec*	ΔFVR (UF + dialysis) *mm Hg/ml/100 ml/sec*
1[b]	43	1.13	−2.0	−7.9	1251	14
2[a]	61	1.16	9.5	2.5	4640	1856
3[a]	56	1.60	7.7	−0.8	113	−1656
4[a]	34	1.35	7.7	−6.8	7332	−200
5[a]	53	1.15	10.0	0.5	2580	102
6[b]	64	[c]	10.7	−3.7	2425	−276
7[b]	41	1.13	7.0	−5.2	620	−124
8[b]	30	1.25	1.6	−5.6	558	275
9[b]	36	1.28	28.3	5.3	7560	1828
10[a]	46	1.40	6.0	2.4	5175	1705
11[a]	43	1.57	14.5	2.2	2094	−172
12[a]	53	1.60	7.1	0.0	6624	1383

Abbreviations are: VR, Valsalva ratio; ΔVT, change in venous tone; and ΔFVR, change in forearm vascular resistance.
[a] Patients treated with isolated UF, sequentially followed by UF + dialysis
[b] Patients treated with UF + dialysis, sequentially following by isolated UF
[c] Valsalva ratio could not be obtained due to atrial fibrillation

VC, decline in plasma volume, and UF rate on the decline in CVP, only VC was significantly related to the decline in CVP ($t = -2.6$; $P < 0.025$), whereas the decline in plasma volume and the UF rate were not.

VC was also inversely related to the decline in plasma volume during UF ($r = -0.66$; $P < 0.025$; Fig. 2), whereas the UF rate ($r = 0.11$) and the colloid osmotic pressure ($r = -0.29$) before dialysis were not. When multivariate regression analysis was used to assess the effect of VC, UF rate and colloid osmotic pressure before dialysis on the fall in plasma volume, only VC was significantly related to the decline in plasma volume ($t = -2.7$; $P < 0.025$), and the other parameters were not.

Protocol B. Reaction of the veins and resistance vessels during isolated UF and UF combined with hemodialysis

The individual data are presented in Table 3 and the summarized data are presented in Table 4.

Blood pressure was significantly higher after isolated UF compared with UF combined with dialysis ($P < 0.05$). The heart rate remained stable during the different treatment modes. Plasma osmolality before the investigation did not differ significantly from the osmolality after isolated UF, whereas the plasma osmolality after UF combined with dialysis was significantly reduced compared with the values before the investigation ($P < 0.05$) and after isolated UF ($P < 0.01$). Plasma colloid osmotic pressure significantly increased both after isolated UF and after UF combined with dialysis compared to the values before the investigation. Values did not differ between isolated UF and UF combined with dialysis. Also the decline in plasma volume was comparable during isolated UF (−7.2 ± 2.7%) and UF combined with dialysis (−5.7 ± 4.9%).

Potassium was 5.2 (±0.5) mmol/liter before the investigation and 4.3 (±0.3) mmol/liter after UF combined with dialysis ($P < 0.005$). Sodium was 138.6 (±3.3) mmol/liter before the investigation and 140.4 (±2.2) mmol/liter after UF combined with dialysis ($P = 0.07$).

Venous tone and FVR differed significantly ($P < 0.001$) between the various treatment modes and were significantly higher during isolated UF ($P < 0.005$) compared to the pretreatment values and to UF combined with dialysis. FVR and

Table 4. Hemodynamic parameters during isolated ultrafiltration and during UF combined with hemodialysis (protocol B)

	Pretreatment	Isolated UF	UF + dialysis	*P*
Mean arterial pressure *mm Hg*	106 (12)	115 (16)[a]	108 (13)	<0.05
Heart rate *beats/min*	70 (7)	70 (6)	69 (8)	0.8
Forearm vascular resistance *mm Hg/ml/100 ml/sec*	3428 (1249)	6842 (3108)[c,d]	3823 (1606)	<0.0001
Venous tone *mm Hg/ml/100 ml*	20.1 (4.8)	29.0 (9.2)[c,d]	18.7 (5.2)	<0.0001
Noradrenaline *nmol/liter*	2.1 (1.8)	2.5 (2.2)	1.9 (0.8)	0.4
Ionized calcium *mmol/liter*	1.25 (0.11)	1.30 (0.11)[b]	1.33 (0.10)[b]	<0.01
Osmolality *mOsm/kg*	312.6 (13.3)	316.9 (12.4)[c]	304.5 (7.6)[b]	<0.05
Colloid osmotic pressure *kPa*	2.7 (0.3)	3.3 (0.5)[d]	3.2 (0.3)[b]	<0.025
Decline in plasma volume %		−7.3 (2.8)[d]	−6.0 (5.4)[d]	

Values are expressed as mean (SD); *P* values are determined by ANOVA.
[a] $P < 0.05$ compared to UF + dialysis
[b] $P < 0.01$ compared to pretreatment values
[c] $P < 0.01$ compared to UF + dialysis
[d] $P < 0.01$ compared to pretreatment values

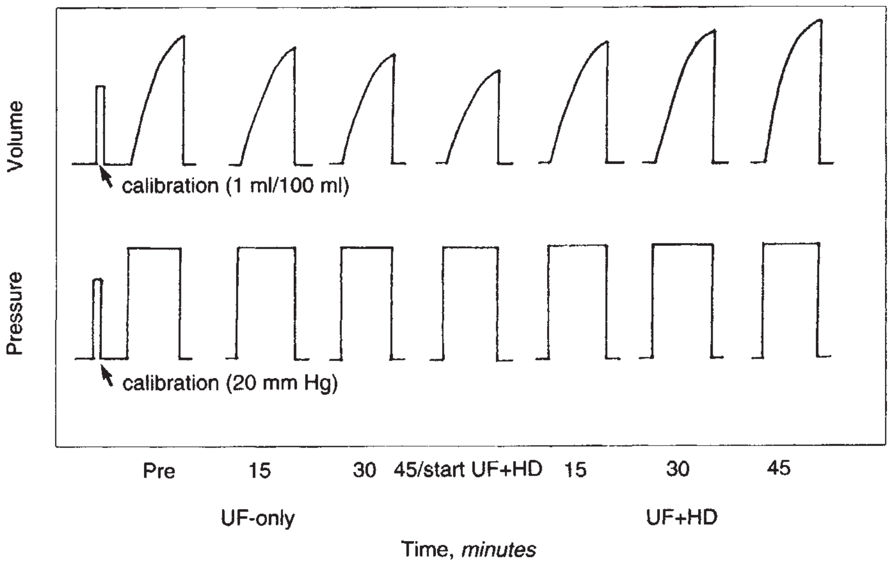

Fig. 3. *Representative measurement of venous tone during isolated UF (UF-only) and UF dialysis (UF + HD).*

venous tone during UF combined with dialysis did not differ significantly compared to the pretreatment state. In several patients, however, venous tone decreased during UF combined with dialysis (Table 3).

In Figure 3 a representative measurement of venous tone in a patient treated with sequential UF dialysis is demonstrated.

Figure 4 illustrates the vascular reaction of patients treated with sequential UF dialysis. Venous tone and FVR increased gradually ($P < 0.05$) during isolated UF and decreased gradually when hemodialysis was started.

In Figure 5, the vascular reaction of patients treated with sequential dialysis-UF is shown. Both venous tone and FVR remained stable during UF combined with dialysis but rose significantly ($P < 0.05$) when isolated UF was performed. In one patient only (no. 1), who responded with a marked venodilation during UF combined with dialysis, venous tone, although obviously increasing during isolated UF, did not reach the pretreatment value.

The noradrenaline levels did not differ significantly between the various treatment modes ($P = 0.4$) due to the large variability. Still, noradrenaline levels tended to rise during UF only and to decrease during UF combined with dialysis.

Ionized calcium differed significantly during the basal state and the different treatment modes ($P < 0.01$), and was significantly higher during isolated UF ($P < 0.05$), and even higher during UF combined with dialysis ($P < 0.05$) compared to the pretreatment state.

The mean Valsalva ratio of the patients was 1.28 (±0.18). The Valsalva ratio was not significantly related to the change in venous tone and FVR during isolated UF ($r = -0.47$; $P = 0.08$ and $r = -0.31$, respectively) and during UF combined with dialysis ($r = -0.23$ and $r = 0.01$; respectively). The age of the patients was not significantly related to the vascular response during the different treatment modes.

Discussion

In this study the effect of VC on hemodynamics was evaluated during isolated UF. Furthermore, in a second protocol, the reaction of the veins and resistance vessels was assessed during isolated UF and UF combined with hemodialysis.

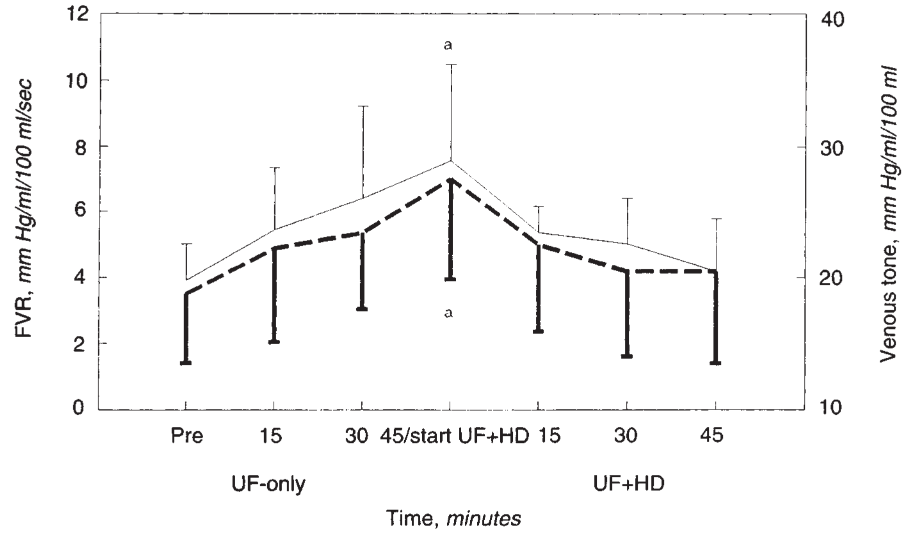

Fig. 4. *Venous and arterial reaction during sequential UF-dialysis (HD).* Symbols are: (——) FVR; (– –) venous tone. Values are expressed as mean (SD). [a] $P < 0.05$ compared to all other measurements.

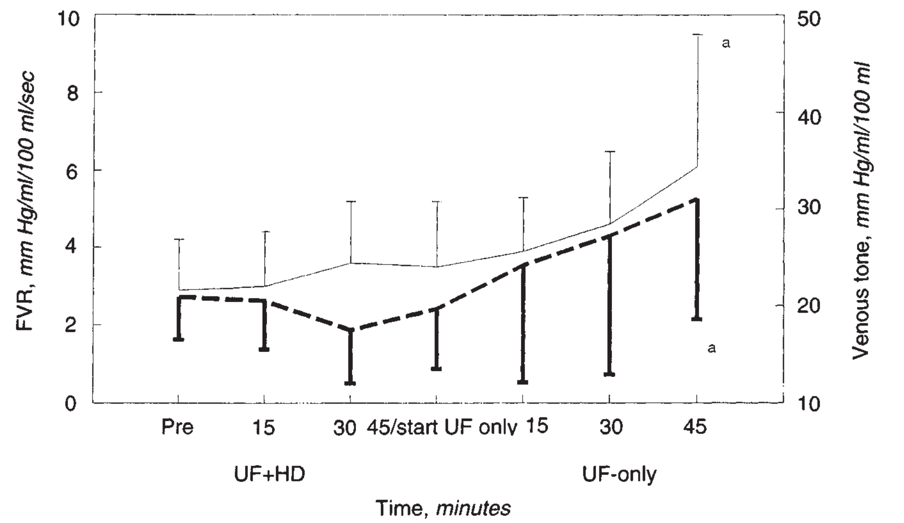

Fig. 5. *Venous and arterial reaction during sequential dialysis (HD)-UF.* Symbols are: (——) FVR; (– –) venous tone. Values are expressed as mean (SD). [a] $P < 0.05$ compared to all other measurements.

In the first protocol, the influence of VC on the fall in CVP and the decline in plasma volume was studied during isolated UF instead of during UF combined with hemodialysis because the alterations in osmolality and acid-base status during the latter may be confounding factors in the assessment of changes in CVP and preservation of plasma volume [1, 2]. As expected, osmolality did not change during isolated UF. During the investigation, CVP and plasma volume declined whereas the colloid osmotic pressure increased. The rise in colloid osmotic pressure was highly significantly related to the fall in plasma volume, which is in accordance with the results of Rodriguez, Pederson and Llach [16].

VC was measured in the forearm by strain gauge plethysmography the day after hemodialysis at normovolemia. VC assessed under such basal circumstances reflects the true viscoelastic properties of the venous wall [17], which are mainly determined by its connective tissue elements [18]. However, as will be discussed later, venous smooth muscle tone increases during isolated UF which can also influence VC to some extent. Because an increase in smooth muscle tone merely leads to a mobilization of hemodynamically inactive blood volume [4], the hemodynamic influence of this effect on VC will probably be minor.

In this study the compliance of the forearm veins was measured. An estimation of the compliance of the systemic circulation is possible by rapidly infusing and withdrawing 500 to 800 ml of blood while measuring the change in CVP [19], however, the burden thus inflicted on the often already compromised cardiovascular system of hemodialysis patients is too large to be ethically justified. As Safar et al have shown a highly significant correlation between peripheral venous compliance and systemic compliance in healthy subjects [19]; in this study only peripheral venous compliance was measured. VC can be influenced by the age of the patient [20]. Also in this study an inverse relationship between VC and age was observed, which, however, did not reach significance. As shown in the present and in a previous study [6], the main determinant for VC in hemodialysis patients is the existence of hypertension.

In the present study, VC was inversely related to the fall in CVP during UF. Multivariate regression analysis showed that this relation remained also present when corrected for the decline in plasma volume. The larger fall in CVP associated with a decrease in VC can be explained by the reduced volume/pressure relationship of the venous system: a minor fall in plasma volume may thus lead to a relatively large fall in CVP [4]. The opposite is also true: when plasma volume increases, the concomitant rise in CVP is inversely correlated with VC [19]. This view is indirectly supported by the finding that VC was inversely correlated to CVP at the beginning of the measurements. Thus, in case of a reduced VC, the venous system is more sensitive to changes in plasma volume. Anecdotical confirmation of the present results was found in a study of Jahn, Schohn and Schmitt [21] who, although they did not measure venous compliance directly, observed a much larger decrease in pulmonary arterial pressure in a patient with severe hypertension compared with a normotensive patient after an equal decline in body weight.

An inverse correlation between VC and the decline in plasma volume was also observed in the present study. A reduced VC can impair plasma volume preservation by disturbing the capillary Starling equilibrium [5]. During UF, the preservation of plasma volume is highly dependent upon the refill of plasma volume from the interstitial fluid [1]. A reduction in VC interferes with this mechanism because the ratio between plasma volume and interstitial volume is decreased [5]. Furthermore, for a given level of plasma volume, the pressure in the postcapillary venules is higher, which increases hydrostatic pressure over the capillary wall and thus impairs refill of plasma volume from the interstitium [5].

Of course, VC is not the only factor which may influence plasma volume preservation during UF; the colloid osmotic pressure before dialysis, the rate of UF and the degree of interstitial hydration all play a role [1, 2]. However, the colloid osmotic pressure before dialysis did not correlate with the decline in plasma volume. Possibly the change in colloid osmotic pressure during a decline in plasma volume is of greater importance for the refill of plasma volume from the interstitium than the absolute value before dialysis [22].

The rate of UF varied only between 1000 and 1500 ml/hr. Moreover, when evaluated by multivariate regression analysis, the influence of the UF rate on plasma volume preservation was small, which is in accordance with the study of Mann et al [23]. The effect of interstitial hydration on plasma volume preservation is most important when patients are ultrafiltrated below their dry weight, when the interstitial fluid is relatively depleted [24]. Patients entered the study exceeding their dry weight by 1 to 3 kg, as assessed by echography of the inferior caval vein, while great attention was paid to prevent underhydration of the patients. When patients are hyper- or normovolemic, the interstitium is well hydrated. Furthermore, in the hypervolemic state, the compliance of the interstitium is probably higher [25], and therefore, large changes in interstitial volume will not have a great impact on interstitial pressure. This means that refill based on this interstitial pressure is relatively independent of the fluid status in the hypervolemic period.

The effect of a reduced VC on both plasma volume preservation and fall in central venous pressure may seem somewhat contradictory, because one would think that after a fall in venous pressure, hydrostatic pressure over the capillary wall would decrease, leading to an increased refill of plasma volume from the interstitium. Furthermore, the impairing effect of a reduced venous compliance on plasma volume preservation occurred despite a significant increase in colloid osmotic pressure. However, as Fauchald [22] has shown, refill of plasma volume from the interstitium is low during the first part of UF, until, after 60 to 120 minutes, the rise in colloid osmotic pressure becomes high enough to result in a near steady state between refill of plasma volume from the interstitium and fluid removal. The UF rate used in his study was ±1200 ml/hr, which is comparable to the rate used in our study. Furthermore, after a fall in venous pressure, it might also take a significant time before the capillary hydrostatic forces reach a new equilibrium [26]. Therefore, in the beginning of UF treatment, the refill of plasma volume from the interstitium will be merely dependent upon the capillary Starling equilibrium present before the start of UF, for which VC is an important determining factor.

In the second protocol, the active reaction of the venous system and resistance vessels was evaluated during isolated UF only and during UF combined with bicarbonate dialysis. The reaction of the venous system was measured at a cuff pressure of 40 mm Hg, because at these transmural pressures, changes in arm volume only reflect active venoconstriction, whereas the contribution of passive venoconstriction, resulting from elastic recoil of the venous wall is negligible [27].

Six patients were studied when isolated UF was sequentially followed by UF combined with dialysis, and in six patients the measurements were started with UF combined with dialysis, followed by isolated UF. This was done to ensure that a difference in vascular reaction between the two treatment modalities would not arise from large differences in plasma volume. Antihypertensive medication was stopped 48 hours before the investigation. However, the drugs used have little effect on the venous system [28]. Furthermore, because the vascular reaction observed did not differ between treated and untreated patients, the use of antihypertensive medication is not likely to have been a disturbing factor.

Whereas osmolality significantly decreased after UF combined with dialysis compared to the values before the investigation and after isolated UF, the rise in colloid osmotic pressure and the decline in plasma volume were equal after both procedures, which is in accordance with the study of Rodriguez, Pederson and Llach [16].

Regardless of whether the investigation was started with isolated UF or with UF combined with dialysis, the increase in venous tone and FVR was significantly higher during isolated UF compared with UF combined with dialysis. As is shown in Table 3, in several patients even a venodilation ensued during UF combined with dialysis. This is in accordance with earlier studies [29, 30]. However, only in the present study and in that of Bradley et al [29] was bicarbonate used as dialysate buffer. A reduced active venoconstriction may lead to pooling of blood and thus to a decrease in cardiac filling pressure.

In addition to active venoconstriction, the mobilization of unstressed blood volume by passive venoconstriction is also very important in the regulation of venous return in case of a decrease in plasma volume. Passive venoconstriction occurs by the de Jager-Kroch phenomenon [3]; that is, when blood flow through a compliant vascular bed decreases, its capacity decreases due to passive elastic recoil. Blood flow through the postcapillary vascular bed declines when precapillary resistance rises. Therefore, the increase of FVR during isolated UF not only leads to the maintenance of blood pressure at the precapillary side of the circulation but also helps to maintain venous return to the heart by passive mobilization of the unstressed blood volume.

Thus, in contrast to isolated UF, the venous reaction during bicarbonate dialysis is reduced both through a decreased active and passive venoconstriction. The cause for the diminished vascular response during bicarbonate dialysis is still unresolved. An insufficient rise of catecholamines [31], an acute reduction of vascular sensitivity to the effect of catecholamines [8], rapid electrolyte shifts [32] and a rise in core temperature [2] may be involved in the pathogenesis of the decreased sympathetic and vascular response during hemodialysis. In the present study, although not significantly, noradrenaline levels tended to rise during isolated UF but to decrease during the subsequential dialysis. However, noradrenaline levels indicate sympathetic activity only indirectly, because only the amount flowing over of the synaptic cleft into the blood is measured [33] and not the concentration present at the nerve terminal itself.

In addition, the reactivity of the vascular wall to sympathetic stimulation may also be influenced by changes in ionized calcium. Ionized calcium is crucial for the contraction of vascular smooth muscle cells [34]. Despite a net influx of calcium from the dialysate into the blood, rapid changes in the acid base status of the patient may lead to decreased levels of ionized calcium during dialysis [35]. However, in the present study, ionized calcium increased significantly during UF combined with dialysis, even to a larger degree than can be explained by plasma volume contraction alone.

Rapid changes in the electrolyte status may also influence sympathetic activity during hemodialysis. Henrich et al [32] observed a decline in catecholamine levels when plasma potassium decreased whereas catecholamine levels remained stable when plasma potassium was kept constant. In our study, the potassium levels decreased only moderately whereas no patient was hypokalemic after the investigation. However, the decrease in osmolality might play a role in the reduced vascular reaction during UF combined with dialysis.

That temperature may play a role in the inadequate vascular reaction during dialysis is supported by studies in which greater hemodynamic stability was observed during dialysis with cooled dialysate [36, 37]. This theory clearly needs further investigation.

The Valsalva ratio was not related to the increase in venous tone or to the rise in FVR, neither during UF only, nor during UF combined with dialysis. Therefore, tests studying heart rate responses in hemodialysis patients are not predictive for the vascular reaction during a decline in plasma volume.

Conclusion

A decrease in VC leads to a steeper fall in CVP and to a larger decline in plasma volume during UF. When the plasma volume decreases, the vascular resistance has to rise and blood has to be mobilized by active and passive venoconstriction in order to maintain hemodynamic stability. The intact cardiovascular regulation mechanisms explain the excellent preservation of arterial pressure observed during isolated UF [8].

During hemodialysis, the reaction of the veins as well as that of the resistance vessels is diminished. If the decline in plasma volume is not too large and if the cardiac function of the patients is not impaired, the reduced vascular reaction does not always lead to hemodynamic instability, as shown in the present study. However, in patients with severe cardiac impairment or in those with decreased left ventricular compliance, who are highly dependent upon adequate cardiac filling pressures [38], a reduction in venous compliance and the diminished vascular reaction during hemodialysis are very likely important contributing factors to the induction of hypotensive periods during hemodialysis.

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